REMARKS

Claim Amendments

Claims 1, 2, 4 and 14-17 have been amended to recite "as measured by ^{1}H NMR spectrometry." Support for the amendment can be found throughout the specification, for example, at page 21, line 34 through page 22, line 4.

Claims 1-5 have been amended to correct a number of typographical errors and to correct antecedent basis errors.

Claim 1 has been amended to recite the phrase "comprising preparing a nucleic acid array on a support."

Claims 12 and 13 have been amended to depend from Claim 3.

No new matter has been added.

Priority Claim

Applicants note that the Examiner has listed the filing date of the provisional application to which priority is claimed as 3 March 2000. The correct filing date of provisional application 60/190,166 is March 17, 2000.

Objection to the Specification

The Examiner objects to the specification because at page 18, lines 3 and 23-24, U.S. Application No. 08/630,148 is referred to as a copending application.

Applicants have removed the phrase "copending" from the two paragraphs on page 18. Withdrawal of the objection is respectfully requested.

Objection to Claim 2

Claim 2 has been objected to becuase in step (c) "linked" is misspelled as "link."

Applicants have amended the claim to correct the spelling error. Withdrawal of the objection is respectfully requested.

Rejection of Claims 1-20 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

A. Claims 1-20

The Examiner states that Claims 1-20 are indefinite, alleging that Claim 1 does not recite method steps of array preparation. The Examiner suggests amending Claim 1 to recite positive and active method steps of array preparation.

Claim 1 has been amended to additionally recite the phrase "comprising preparing a nucleic acid array on a support."

One skilled in the art would immediately recognize that there are multiple methods of synthesizing a nucleic acid array on a support, and that the essence of each method is contacting the support with the nucleoside phosphoramidite monomers. The present application, at page 7, lines 1-24, teaches that nucleic acid arrays can be prepared using a variety of synthetic techniques, including light-methods, flow channel or spotting methods, pin-based methods, bead-based methods or combinations thereof. Thus, it would be clear to one skilled in the art that there are multiple ways of preparing a nucleic acid array and that the claim properly encompasses methods that have the common step of contacting a support with a nucleoside monomer.

B. Claims 1-20

The Examiner states that Claims 1-20 are indefinite for the recitation "said synthesizing" in Claim 1. Claim 1 has been amended to replace "synthesizing" with "method," as suggested by the Examiner.

C. Claim 2

The Examiner states that Claim 2 is indefinite for the recitation "said synthesizing." "Said synthesizing" has been replaced with "said method," which finds antecedent basis in Claim 1.

D. Claim 2

The Examiner states that Claim 2 is indefinite in step (b) for the phrase "first region." Claim 2 has been amended to replace "first region" with "said region," as suggested by the Examiner. This amendment does not narrow the scope of the claim.

E. Claim 2

The Examiner states that Claim 2 is indefinite in step (c) because "used" lacks antecedent basis. "Used" has been replaced with "attached," which finds antecedent basis in step (b). This amendment does not narrow the scope of the claim.

F. Claim 3

The Examiner states that Claim 3 is indefinite for the recitation "said synthesizing." "Said synthesizing" has been replaced with "said method," which finds antecedent basis in Claim 1.

G. Claim 3

The Examiner states Claim 3 is indefinite because it is unclear whether the first area and second area of steps (a) and (b) are the same as or different from the first area and second area of steps (c) and (d).

Applicants disagree that this recitation of Claim 3 is unclear and note that steps (c) and (d) of the claim recite "said first area" and "said second area," which find antecedent basis in the first and second areas recited in steps (a) and (b). The recitation of "said" clearly indicates that the first and second areas of steps (c) and (d) are the same as the first and second areas of steps (a) and (b). Applicants believe that these phrases are clear and definite as written.

H. Claims 12-13

The Examiner states that Claims 12 and 13 are indefinite because the recitation "each different nucleic acid" lacks antecedent basis in Claim 5.

Claims 12 and 13 have been amended to depend upon Claim 3. Claim 3, in step (e), recites "at least 100 nucleic acids having different sequences," thereby providing antecedent basis for the recitations of Claims 12 and 13.

Applicants believe that the claims, as amended, even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-20 Under 35 U.S.C. § 102(a)

Claims 1-20 are rejected under 35 U.S.C. § 102(a) as being anticipated by McGall, *et al.* (U.S. Patent No. 6,022,963; Reference 40). The Examiner states that McGall, *et al.*, disclose a method of preparing a nucleic acid array on a support wherein each nucleic acid occupies a separate known region of the support, where the protected nucleoside phosphoramidite monomers are "pure phosphoramidite."

Rejection under 35 U.S.C. § 102(a) in view of McGall, *et al.*, is improper according to MPEP § 2132.01, which states:

> Note that when the reference is a U.S. patent published within the year prior to the application filing date, a 35 U.S.C. 102(e) rejection should be made.

The effective filing date of the present application is March 17, 2000, based on entitlement to priority to U.S. Serial No. 60/190,166, as acknowledged by the Examiner. McGall, *et al.*, is a U.S. patent issued on February 8, 2000, less than one year before the effective filing date of the subject application. Thus, McGall, *et al.*, should be treated as § 102(e) prior art in accordance with MPEP § 2132.01.

Applicants respectfully disagree that the present claims are anticipated by McGall, *et al.* The meaning of "pure phosphoramidites" is not defined in the McGall, *et al.*, patent. In particular, the means by which purity was assessed is not disclosed. The present application teaches that the *method of purity determination is crucial* to practicing the claimed method.

Example 1 on pages 21 and 22 of the specification teaches that one lot of MeNPOC-N^4-isobutyryl-2'-deoxycytidine-CEP was used in a coupling efficiency test to make a 6-mer. The phosphoramidite nucleoside failed the efficiency test, as the synthesis yielded only 14% of the control synthesis, which corresponds to a coupling efficiency of only about 2.8-3.6%. No impurity in the MeNPOC-N^4-isobutyryl-2'-deoxycytidine-CEP was detectable by HPLC or ^{31}P NMR spectrometry; however, an impurity was noted in the ^1H NMR spectrum. This impurity

was determined to correspond to about 3-5 % mole of $(MeO)(NCCH_2CH_2O)PN(iPr)_2$. Subsequent chromatographic purification of the phosphoramidite nucleoside (see Example 2, page 22) yielded a product that had no impurity detectable by either ^1H or ^{31}P NMR spectrometry. The purified phosphoramidite nucleoside had a coupling efficiency of about 16-32% (Example 1).

Examples 1 and 2 thus demonstrate that the exact definition of "pure" in the context of phosphoramidite nucleosides is crucial. While a phosphoramidite nucleoside might be "pure" when analyzed by one method (e.g., HPLC, ^{31}P NMR), it may have a significantly lower coupling efficiency than a phosphoramidite nucleoside whose purity has been verified by ^1H NMR spectrometry. Therefore, the recitations that the nucleoside phosphoramidite monomers of the present invention have less than 1.0 mole % or less than 0.5 mole % or less than 0.2 mole % phosphoramidite contaminant as measured by ^1H NMR spectrometry distinguishes the instant subject matter from that taught by McGall, *et al.* Although McGall, *et al.* recognized the general desirability of a "pure" oligonucleoside, there is no teaching or suggestion of the exact level of purity required to obtain a oligonucleoside phosphoramidite monomer that exhibits substantially greater coupling efficiency in nucleic acid array preparation. Accordingly, McGall, *et al.*, does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 1-20 Under 35 U.S.C. § 103(a)

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being obvious over McGall, *et al.* As discussed above, McGall, *et al.*, is properly treated as a reference under 35 U.S.C. § 102(e), not 35 U.S.C. § 102(a). Under 35 U.S.C. § 103(c), subject matter developed by another which qualifies as prior art only under subsections (e), (f), and/or (g) of section 102 shall not preclude patentability under § 103 where the subject matter and the claimed invention were owned by the same person at the time the invention was made.

Applicants hereby state for the record that the claimed invention and the subject matter of McGall, *et al.*, were owned by the same person (Affymetrix, Inc.) at the time the invention was made. Therefore, McGall, *et al.*, does not preclude patentability under 35 U.S.C. § 103(a). Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-15 and 18-20 Under 35 U.S.C. § 103(a)

Claims 1-15 and 18-20 are rejected under 35 U.S.C. § 103(a) as obvious over Fodor, *et al.* (U.S. Patent No. 5,800,992; Reference 35), in view of Srivastava, *et al.* (U.S. Patent No. 5,525,719; Reference A). The Examiner states that Fodor, *et al.*, teach a method of preparing a nucleic acid array on a support. The Examiner acknowledges that Fodor, *et al.*, do not teach the purity of the phosphoramidite monomers. The Examiner states that Srivastava, *et al.*, teach that pure phosphoramidite monomers are critical for synthesizing nucleic acids to be used in biological applications.

Srivastava, *et al.*, teach that the purity of phosphoramidite monomers was analyzed by ^{31}P NMR spectrometry (column 5, lines 27-28 and 40-42). As discussed above, ^{31}P NMR spectrometry is inadequate to determine whether phosphoramidite monomers are of sufficient purity for efficient coupling in nucleic acid array preparation. The instant application teaches that a monomer that appears "pure", as assessed by ^{31}P NMR spectrometry, could have a 5- to 10-fold lower coupling efficiency than a monomer found to be "pure" by ^{1}H NMR spectrometry. Although Srivastava, *et al.*, disclose that the *structural identity* was determined by ^{1}H NMR spectrometry (column 5, lines 40-42), there is no disclosure of the use of ^{1}H NMR spectrometry to assay *purity*. Thus, the level of purity of the phosphoramidite monomers of Srivastava, *et al.*, would not have been clear to the ordinarily skilled artisan. At best, Srivastava, *et al.*, teach that phosphoramidite monomers which have a higher degree of purity are preferred to phosphoramidite monomers having a lower degree of purity for use in nucleic acid synthesis for biological applications. There is no teaching or suggestion of any particular degree of purity, and as shown in the instant application, a determination of the degree of purity can vary depending upon the method of assessment. In fact, Srivastava, *et al.*, do not teach the use of an assessment method sufficient to determine the degree of purity of the monomers with the requisite sensitivity. Accordingly, even assuming *arguendo* the combination of Fodor, *et al.*, with Srivastava, *et al.*, the combination does not teach or suggest the claimed methods utilizing phosphoramidite monomers having phosphoramidite contaminant in an amount of less than about 1.0 mole%, less than 0.5 mole % or less than about 0.2 mole %. Thus, the cited references do not render the claimed invention obvious. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 16 and 17 Under 35 U.S.C. § 103(a)

Claims 16 and 17 are rejected under 35 U.S.C. § 103(a) as being obvious over Fodor, *et al.*, in view of Srivastava, *et al.*, and Pirrung, *et al.* (U.S. Patent No. 5,908,926; Reference B). The Examiner relies on the teachings of Fodor, *et al.*, and Srivastava, *et al.*, which were discussed *supra*, and states that Pirrung, *et al.*, teaches the MeNPOC protecting group.

As discussed above, the combination of Fodor, *et al.*, and Srivastava, *et al.*, do not teach or suggest the claimed invention. Pirrung, *et al.*, do not teach or suggest monomers having the recited purity and thus do not remedy the defects of Fodor, *et al.*, and Srivastava, *et al.* Reconsideration and withdrawal of the rejection are requested.

Double Patenting

Claims 1-17 are rejected under obviousness-type double patenting over McGall, *et al.* The Examiner states that the claims of the application and the patent are not distinct because both sets of claims are drawn to methods of synthesizing a plurality of nucleic acids on a support. The Examiner further states that the "pure phosphoramidites" disclosed by McGall, *et al.*, inherently have less than 1 mole % of phosphoramidite contaminant.

Applicants refer to the discussion above regarding the meaning of the term "pure." "Pure" is a relative term and is dependent, for example, on the technique used to determine purity. The instant application demonstrates that a phosphoramidite monomer found to be "pure" by HPLC and ^{31}P NMR spectrometry contains a significant amount of phosphoramidite contaminant (about 3-5 % mole). Thus, "pure" as used in McGall, *et al.*, cannot be construed to inherently mean less than 1% contaminant. Applicants have discovered that purity determination by ^{1}H NMR spectrometry is critical to accurately assessing the purity of a phosphoramidite monomer, such that the recitation that purity is determined by ^{1}H NMR spectrometry patentably distinguishes the present subject matter from McGall, *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If

the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 18, lines 1 through 4 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

> In addition, novel photoremovable protecting groups such as 5'-O-pyrenylmethyloxy carbonyl (PYMOC) and methylnitropiperonyloxycarbonyl (MeNPOC) have been described in [the copending] U.S. Patent Application Ser. No. 08/630,148, filed April 10, 1996, the contents of which are hereby incorporated by reference.

Replace the paragraph at page 18, lines 21 through 24 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

> In addition to the above-described references, photocleavable protecting groups and methods of using such photocleavable protecting groups for polymer synthesis have been described in [the copending applications] U.S. Patent Application Ser. Nos. 08/630,148 (filed April 10, 1996) and 08/812,005 (filed March 5, 1997) which are incorporated by reference herein.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method of preparing a nucleic acid array on a support comprising preparing a nucleic acid array on a support, wherein each nucleic acid occupies a separate known region of the support, said method [synthesizing] comprising contacting said support with protected nucleoside phosphoramidite monomers having less than about 1 mole % of a phosphoramidite

contaminant, as measured by ^{1}H NMR spectrometry, selected from the group consisting of $(MeO)(NCCH_2CH_2O)PN(iPr)_2$, $(MeO)P(N(iPr)_2)_2$, $(MeO)_2PN(iPr)_2$, and $(NCCH_2CH_2O)_2PN(iPr)_2$.

2. (Amended) A method in accordance with claim 1, said method [synthesizing] further comprising:

(a) activating a region of the support;

(b) attaching a nucleotide to said [a first] region, said nucleotide having a masked reactive site linked to a protecting group;

(c) repeating steps (a) and (b) on other regions of said support whereby each of said other regions has bound thereto another nucleotide comprising a masked reactive site linked [link] to a protecting group, wherein said another nucleotide may be the same or different from that attached [used] in step (b);

(d) removing the protecting group from one of the nucleotides bound to one of the regions of the support to provide a region bearing a nucleotide having an unmasked reactive site;

(e) binding an additional nucleotide to the nucleotide having [with] an unmasked reactive site; and

(f) repeating steps (d) and (e) on regions of the support until a desired plurality [pluarlity]of nucleic acids is synthesized, each nucleic acid occupying separate known regions of the support; [and]

wherein said phosphoramidite contaminant is present in an amount of less than about 0.5 mole % as measured by ^{1}H NMR spectrometry.

3. (Amended) A method in accordance with claim 1, wherein said method [synthesizing] comprises the sequential steps of:

(a) generating a pattern of light and dark areas by selectively irradiating at least a first area of a surface of a substrate, said surface comprising immobilized nucleotides on said surface, said nucleotides capped with a photoremovable protecting [protective] group,

without irradiating at least a second area of said surface, to remove said protecting [protective] group from said nucleotides in said first area;

(b) simultaneously contacting said first area and said second area of said surface with a first nucleotide to couple said first nucleotide to said immobilized nucleotides in said first area, and not in said second area, said first nucleotide capped with said photoremovable protecting [protective] group;

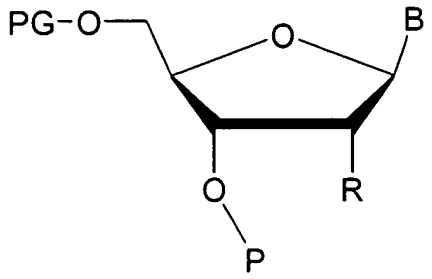
(c) generating another pattern of light and dark areas by selectively irradiating with light at least a part of said first area of said surface and at least a part of said second area to remove said protecting [protective] group in said at least a part of said first area and said at least a part of said second area;

(d) simultaneously contacting said first area and said second area of said surface with a second nucleotide to couple said second nucleotide to said immobilized nucleotides in at least a part of said first area and at least a part of said second area; and

(e) performing additional irradiating and nucleotide contacting and coupling steps so that a matrix array of at least 100 nucleic acids having different sequences is formed on said support.

4. (Amended) A method in accordance with claim 1, wherein said contaminant is present in an amount of less than about 0.2 mole % as measured by ^{1}H NMR spectrometry.

5. (Amended) A method in accordance with claim 1, wherein said protected nucleoside phosphoramidite monomers have the formula:



wherein

B is a member selected from the group consisting of adenine, guanine, thymine, cytosine, uracil and analogs thereof;

R is a member selected from the group consisting of hydrogen, hydroxy, protected hydroxy, halogen and alkoxy;

P is a phosphoramidite group; and

PG is a [photoremoveable protected] photoremovable protecting group.

12. (Amended) A method in accordance with claim 3 [5], wherein each different nucleic acid is in a region having an area of less than about 1 cm^2.

13. (Amended) A method in accordance with claim 3 [5], wherein each different nucleic acid is in a region having an area of less than about 1 mm^2.

14. (Amended) A method in accordance with claim 5, wherein said phosphoramidite contaminant is present in an amount of less than 0.2 mole % as measured by ^{1}H NMR spectrometry.

15. (Amended) A method in accordance with claim 5, wherein B is selected from the group consisting of adenine, guanine, cytosine and thymine, R is hydrogen, and said phosphoramidite contaminant is present in an amount of less than 0.2 mole % as measured ^{1}H NMR spectrometry.

16. (Amended) A method in accordance with claim 5, wherein B is selected from the group consisting of adenine, guanine, cytosine and thymine, R is hydrogen, PG is MeNPOC and said phosphoramidite contaminant is present in an amount of less than 0.2 mole % as measured ^{1}H NMR spectrometry.

17. (Amended) A method in accordance with claim 5, wherein B is selected from the group consisting of adenine, guanine, cytosine and thymine, R is hydrogen, PG is MeNPOC, P is $-P(OCH_2CH_2CN)N(iPr)_2$ and said phosphoramidite contaminant is present in an amount of less than 0.2 mole % as measured ^{1}H NMR spectrometry.